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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/973,473	10/09/2001	Nahum Sonenberg	514012000400	5331

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EXAMINER

MARVICH, MARIA

ART UNIT PAPER NUMBER

1636

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/973,473	Applicant(s) SONENBERG ET AL.	
	Examiner Maria B Marvich, PhD	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 1-6 and 21-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 October 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3/20/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 7/21/03.

Claims 1-41 are pending in the instant application.

Election/Restrictions

Applicant's election without traverse of Group II (claims 7-20) in the amendment filed 7/21/03 is acknowledged. Claims 1-6 and 21-41 have been withdrawn as drawn to non-elected subject matter. Claims 7-20 are under examination in this office action.

Information Disclosure Statement

An IDS filed 3/20/03 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the address of Nahum Sonenberg has been altered.

Specification

The drawings are objected to because Figure 1 has four parts, A-D. However, figure 1D is not described in the Brief Description of Drawings. Figure 5 has three parts, A-C. However,

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figure 5C is not described in the Brief Description of Drawings. The Brief Description of Drawings describes figure 4C. However, figure 4 only has a part A and B.

The abstract of the disclosure is objected to because eIF-4E, FRAP, mTOR and PI3 are abbreviated. These should be spelled out for clarity. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: on page 24, the text refers to peptides "shown in the figure below". However, the text is not followed by a figure. If there is an existing figure that corresponds to the text, it would be remedial to indicate the appropriate figure. Otherwise, the reference should be deleted.

Appropriate correction is required.

Claim Objections

Claims 8 and 9 are objected to because of the following informalities: 4E-BP and eIF4 are abbreviated and should be spelled out for clarity.

Claim 16 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 15. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9 and 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation "said positive modulator of cap-dependent translation" in claim 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 is vague and indefinite in that the metes and bounds of "eIF-4E sequestering agent" are unclear. It is unclear if the sequestering agent is the same as the agent that is "suspected of being a modulator of cap-dependent translation" or a different agent.

Claim 14 is vague and indefinite in that the metes and bounds of p82, p150, p130 and p20 are unclear. Applicants have not described the preceding peptides such that the metes and bounds of the protein are known. Multiple proteins are known as p20 or p130, however, it is unclear to which of these proteins the claims refer.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modulator of the level of activity of 4E-BP1 and for the

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sequestration of eIF-4F with 4EBP1, does not reasonably provide enablement for increase and/or strengthening of the interaction of 4EBP1 with eIF-4E or for sequestration of eIF4F with any sequestration agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and *In re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention.** The invention is directed to methods of identifying agents that modulate glucose or fat metabolism *in vivo*. The invention utilizes disciplines of pharmacology, cell biology and clinical technology.

2) **Scope of the invention.** The claims specifically recite method steps in which an agent is administered to an animal *in vivo* followed by measurement of glucose or lipid in the animal compared to an untreated animal. The agent is intended to disrupt or increase the formation of the eIF-4F pre-initiation complex in dependent claims by administration of agents intended to modulate the level or activity of 4EBP1, increase or strengthen the interaction of 4EBP1 with eIF4, decrease or weaken the interaction of 4EBP1 with eIF4 and decrease the amount of eIF-4F pre-initiation complex. In order to decrease the amount of eIF-4E pre-initiation complex,

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applicants recite use of a sequestration agent with an amino acid sequence selected from SEQ ID NO 21, 22, 23, 24, 26 and 28 or 4E-BP, eIF4G, p82, p150, p130, p20, 4E-BP1, 4EBP2, 4E-BP3, eIF-4G1, eIF-4G2. Therefore, the scope of the instant invention is broad in that the agents that are contemplated for form a large and diverse group.

3) Number of working examples and guidance. Applicants have determined a role for 4EBP1 in fat tissue growth, metabolism of glucose and weight gain by characterization of a 4EBP1 knock out mouse (see example 1-5). Specifically, applicants have developed a 4E-BP1 deficient mouse, analyzed cap-dependent translation, eIF4E phosphorylation, oxygen consumption and metabolic parameters. Furthermore, the prior art has demonstrated a positive correlation between cell growth and translation rates and eIF4E phosphorylation, which taken together indicates to the applicants that 4EBP1 is a mediator of energy homeostasis in animals. Based upon this, applicants have proposed a method for identifying agents that modulate fat and glucose metabolism *in vivo* in animals that include humans.

4) State of Art. The instant invention proposes an *in vivo* screening method for the identification of drugs that modulate glucose and/or fat metabolism. However, the art of targeting eIF4E translational initiation is not a high art. Furthermore, the art of screening drugs in humans is not a high art in the early stages of drug design. Typically, animal models that are established to mimic disease states are used to identify agents specific to a biochemical pathway.

5) Unpredictability of the art. Based upon observations of a 4EBP1 phenotype of 4EBP1 knock out mice, applicants have proposed a method of identifying agents that modulate glucose or fat metabolism that is designed to identify agents that modulate the formation of a pre-initiation complex involving eIF4E. Applicants have specifically targeted the interaction of

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eIF4E with 4EBP. Furthermore, applicants recite use of sequestering agents that are proteins with similar 4E-binding sites. However, applicants have not reduced to practice use of any of the recited sequestration agents except 4EBP1 to alter glucose or fat metabolism *in vivo*. The art of predicting homologous function through homology modeling is highly unpredictable and as taught by Berendsen, effective for only about 25% of the proteins for which the amino acid sequence is known (see e.g. pages 642, col 2) and is a grand challenge of high performance computing (see e.g. page 643, col 1, last paragraph). Therefore, the sequestering ability of any of these proteins other than 4EBP1 is unknown.

Furthermore, applicants recite that the agent to be administered will modulate glucose or fat metabolism by increasing and/or strengthening the interaction of 4eBP1 and eIF4E. However, the ability to identify a drug that can strengthen an interaction is highly unpredictable. Applicants have not indicated how the interaction between 4EBP and eIF4E can be strengthened.

6) **Summary.** The invention recites a single method step of identifying agents that modulate glucose and fat metabolism. The unpredictability of using the claimed invention in *in vivo* drug screens is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbates a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7, 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Rubsamen and Lloyd (US 5, 672,581; see entire document).

Rubsamen and Lloyd teach a method of injecting insulin in vivo and then measuring glucose levels (see e.g. col 10, line 52-65). Insulin has been shown to release 4E-BP1 from eIF-4E therefore reducing the activity of 4E-BP1 as a sequestering agent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 7, 8 and 10-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonenberg et al, (US 5,874,231; see entire document).

Applicants recite a method of identifying an agent, which modulates glucose or fat metabolism in which an agent is administered in vivo followed by analysis of glucose, or lipid levels in comparison to animals not treated.

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Sonenberg et al teach a method of screening for compounds that modulate cap-dependent translation. The agent is used in animal models and human subjects (see e.g. col 25, line 15-27). The method is directed towards identifying drugs useful in the treatment of Diabetes and other hormone disorders, which is characterized by an increase in blood glucose. The system comprises a cellular component, which in a preferred embodiment is 4E-BP1 and a translation factor, which in a preferred embodiment is eIF-4E (see e.g. col 4, line 30-40). The agents are analyzed for their ability to modulate binding between a cellular component and a translation factor (see e.g. col 23, line 12-25). The methods encompassed by the invention can be used to screen agent libraries to discover novel drugs for treating hormone disorders (see e.g. col 24, line 36-39). For example, insulin was tested which decrease the association between 4E-BP1 and eIF-4e (see e.g. col 30, line 64-67). Furthermore, addition of GST-4E-BP1 and GST-4E-BP2 decreased formation of eIF-4e initiation complexes.

Sonenberg et al do not teach that following administration of the agent that modulates cap-dependent translation, glucose or lipid levels are assayed in comparison to an animal not treated with the agent.

It would have been obvious to someone of skill in the art to assay the effects of the agent once introduced into the animal model or human subject by assaying glucose or lipid levels as a means of utilizing the teachings of Sonenberg et al given that the assay of Sonenberg et al is designed to identify Diabetes drugs or treatments and Diabetes drugs are assayed by measuring blood glucose levels. A person of skill in the art would have been motivated to assay glucose levels following administration of an agent as the basis of the agents is to lower glucose levels in the blood and an accurate measurement of blood glucose levels is in comparison to no agent or

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treatment. Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No Claims allowed.

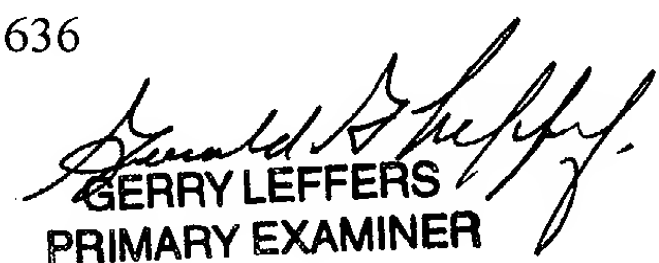
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

October 15, 2004


GERRY LEFFERS
PRIMARY EXAMINER